In Utero Model to Assess the Fate of Transplanted Human Cells for Translational Research and Pediatric Therapies

Grant Award Details

In Utero Model to Assess the Fate of Transplanted Human Cells for Translational Research and Pediatric Therapies

Grant Type: Early Translational I

Grant Number: TR1-01269

Project Objective: To expand CD34 hematopoietic cells and hESCs and transplant into fetal animal models to test engraftment

Investigator:

Name:	Alice Tarantal
Institution:	University of California, Davis
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $3,143,392

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: In Utero Model to Assess the Fate of Transplanted Human Cells for Translational Research and Pediatric Therapies

Public Abstract: nfants with inherited blood diseases (such as sickle cell anemia, thalassemia, bleeding disorders) or other inherited metabolic disorders can be identified early in development using sophisticated diagnostic tests. Currently, the treatment for many of these childhood illnesses may include bone marrow transplantation which is complicated by: (1) the toxicity associated with chemotherapy or radiation-based regimens necessary to ensure the transplanted cells persist; (2) serious health complications associated with rejection of the donor cells; (3) the fact that only ~20-25% of children will have a matched donor, which is even less likely for ethnic populations and underrepresented minorities; and (4) the concern that significant damage, particularly to the brain, has occurred by the time the child is being considered for transplantation. Recent studies suggest that very early treatment before damage from the disease has occurred provides the best survival outcomes, and that immature cell sources may be most effective because they have characteristic features that are more compatible with the developmental stage of the patient. Human umbilical cord blood has been demonstrated to be a very effective source of hematopoietic stem cells (HSC) for transplantation, even if the donor cells do not match the recipient; in these cases the incidence and severity of disease post-transplant has been shown to be very low. However, there are significant limitations to more widespread use of umbilical cord blood HSC because of the low number of cells that are available each time cord blood units are collected. Human embryonic stem cells (hESC) provide another potential source of early stage blood cells for clinical transplantation for young patients. However, there remain significant concerns regarding the safety of use of cells obtained from hESC in all age groups. It is also currently unknown if early blood cells obtained from hESC will provide an advantage over other sources such as umbilical cord blood cells. These studies address crucial bottlenecks that prevent the use of therapeutically important cells for treating pediatric diseases, and methods and models to ensure that proposed approaches will be safe and effective for human use. The bottlenecks to be studied include: (1) the need to treat infants very early in their disease with sufficient and compatible cells; (2) the need to explore methods that will expand umbilical cord blood cells useful for transplantation, and to compare these cells to blood cells obtained from hESC; and (3) the need to use models for humans and related tools that can effectively predict outcome once cells are injected into the body, and to monitor where they travel and ultimately reside and function. The approaches proposed in this application will provide substantial advances in assessing the safety, for example, of new cell-based therapies with hESC, and provide new treatment options for many patients in need.

Statement of Benefit to California:	The benefits to the State of California and its citizens are critically needed effective and safe cellular therapies that could provide potential cures for infants and children diagnosed with an inherited blood cell or metabolic disorder. For example, current statistics on sickle cell disease, the most common inherited blood cell disease in the U.S., indicates approximately 20 children each day (about 8,000 each year) are born with this disease. Sickle cell disease and other blood cell disorders are present in all populations but are more prevalent in persons of African, Mediterranean, Asian, Southeast Asian, Caribbean, and South and Central American origins. The California Newborn Screening Program detects approximately 120 new cases of sickle cell disease every year. Thalassemia, another inherited blood disorder, is considered the most common genetic blood disease worldwide, with recent data indicating approximately 400,000 affected babies born annually. It is one of the most frequent disorders detected yearly in the California Newborn Screening Program of over 700,000 births. Millions of children world-wide suffer from the many serious complications associated with sickle cell disease and thalassemia that decrease life expectancy. These are just two of many inherited blood diseases that could substantially benefit from early treatment, and using stem cells from umbilical cord blood or pluripotent cells obtained from human embryonic stem cells. Similarly, more than 800 children and 400 adults in [REDACTED] alone have been diagnosed with inherited bleeding disorders including hemophilia. With current diagnostic capabilities, infants with these inherited blood diseases can be identified before they are born and cell therapies initiated at this time thus avoiding the damaging effects associated with these diseases. This could provide a means to ensure the delivery of healthy term newborns free of the many postnatal complications of these diseases that diminish quality of life and long-term survival.